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Optimal Cervical Cancer Screening in Women Vaccinated Against Human Papillomavirus

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Abstract

Background: Current US cervical cancer screening guidelines do not differentiate recommendations based on a woman's human papillomavirus (HPV) vaccination status. Changes to cervical cancer screening policies in HPV-vaccinated women should be evaluated.

Methods: We utilized an individual-based mathematical model of HPV and cervical cancer in US women to project the health benefits, costs, and harms associated with screening strategies in women vaccinated with the bivalent, quadrivalent, or nonavalent vaccine. Strategies varied by the primary screening test, including cytology, HPV, and combined cytology and HPV "cotesting"; age of screening initiation and/or switching to a new test; and interval between routine screens. Cost-effectiveness analysis was conducted from the societal perspective to identify screening strategies that would be considered good value for money according to thresholds of $50 000 to $200 000 per quality-adjusted life-year (QALY) gained.

Results: Among women fully vaccinated with the bivalent or quadrivalent vaccine, optimal screening strategies involved either cytology or HPV testing alone every five years starting at age 25 or 30 years, with cost-effectiveness ratios ranging from $34 680 to $138 560 per QALY gained. Screening earlier or more frequently was either not cost-effective or associated with exceedingly high cost-effectiveness ratios. In women vaccinated with the nonavalent vaccine, only primary HPV testing was efficient, involving decreased frequency (ie, every 10 years) starting at either age 35 years ($40 210 per QALY) or age 30 years ($127 010 per QALY); with lower nonavalent vaccine efficacy, 10-year HPV testing starting at earlier ages of 25 or 30 years was optimal. Importantly, current US guidelines for screening were inefficient in HPV-vaccinated women.

Conclusions: This model-based analysis suggests screening can be modified to start at later ages, occur at decreased frequency, and involve primary HPV testing in HPV-vaccinated women, providing more health benefit at lower harms and costs than current screening guidelines.

In 2012, cervical cancer screening guidelines were harmonized across major guideline-making organizations (1,2), emphasizing two provisions that marked a trend toward less intensive screening: 1) routine cervical screening should not begin before age 21 years, irrespective of age of sexual initiation, and 2) routine cytology testing should not occur more frequently than every three years, with an option to switch to cytology and HPV testing ("cotesting") every five years at age 30 years. These changes have been motivated by a better understanding of the role of human papillomavirus (HPV), a highly prevalent sexually transmitted infection, in the development of cervical cancer.

With the availability of HPV vaccines and recommendations for routine vaccination of young girls since 2007, the burden of cervical cancer is expected to decrease, providing even more opportunity to further revise screening guidelines. The bivalent and quadrivalent vaccines target the two most carcinogenic HPV types, 16 and 18, which contribute to roughly 70% of cervical cancer cases worldwide; the quadrivalent vaccine also

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Table 1. Cervical cancer screening strategies*

Screening start age, y	Screening test†	Interval‡	Switch age, y	Screening test after switch age†	Interval after switch age‡
Women vaccinated with HPV-2 or HPV-4					
21, 25, 30, 35	Cytology	3-y, 4-y, 5-y	–	–	–
25, 30, 35	HPV test	3-y, 5-y	–	–	–
25, 30, 35	Cotest	5-y	–	–	–
21	Cytology	3-y	30	HPV test	3-y, 5-y
21	Cytology	3-y	30	Cotest	5-y
Women vaccinated with HPV-9					
21, 25, 30, 35	Cytology	3-y, 4-y, 5-y, 10-y 3-time (ages 35, 40, 45 y), 2-time (ages 35, 40 y), 1-time (age 40 y)	–	–	–
25, 30, 35	HPV test	3-y, 5-y, 10-y 3-time (ages 35, 40, 45 y), 2-time (ages 35, 40 y), 1-time (age 40 y)	–	–	–
25, 30, 35	Cotest	5-y, 10-y 3-time (ages 35, 40, 45 y), 2-time (ages 35, 40 y), 1-time (age 40 y)	–	–	–
21	Cytology	3-y	30	HPV test	3-y, 5-y
21	Cytology	3-y	30	Cotest	5-y

*Human papillomavirus (HPV)–2, HPV-4, and HPV-9 refer to the bivalent, quadrivalent, and nonavalent HPV vaccines, respectively. HPV = human papillomavirus.
†HPV testing strategy involves detection of high-risk HPV types with HPV-16/18 genotype information; cotesting strategy involves combined cytology and HPV testing for primary screening; routine screening for all strategies ends at age 65 years. Management of women with abnormal screening results was assumed to follow clinical guidelines and includes: for cytology testing, reflex HPV testing for women with atypical squamous cells of undetermined significance (ASCUS) and referral to colposcopy for women with more severe abnormal results; for HPV testing, referral to colposcopy for women positive for HPV-16/18 and cytology triage for women positive for other high-risk HPV (those with ASCUS or worse are referred to colposcopy, while those with normal cytology return for follow-up testing in 12 months); and for cotesting, HPV-16/18 genotype testing for women with cytology-negative, HPV-positive results (1,21,22).
‡Interval indicates time between routine screens. 1-time, 2-time, and 3-time indicate screening one time, two times, and three times per lifetime, respectively, at ages indicated.

targets noncarcinogenic HPV types 6 and 11, which cause most genital warts. In clinical trials, both vaccines have demonstrated nearly 100% protection against vaccine-type infections and high-grade precancers in recipients who had received all three doses prior to HPV exposure (3–5). A nonavalent vaccine targeting seven carcinogenic types that contribute to 90% of cervical cancer cases (HPV-16/18/31/33/45/52/58) plus HPV-6/11 has recently been licensed and recommended based on evidence of similarly high vaccine efficacy and immunogenicity (6,7).

Despite the expectation that HPV vaccination will reduce cervical cancer risk among recipients, current guidelines do not differentiate cervical screening recommendations based on a woman's vaccination status. Reasons against changing screening policy in HPV-vaccinated women have include: 1) the low uptake of HPV vaccination in the United States, below 50% for completion of all three doses (8); 2) uncertain quality of documentation for an individual's vaccination history (ie, type of vaccine received, vaccination age, dosage timing); and 3) limited observations of real-world vaccine effectiveness in reducing prevalence of infection and precancer (9). However, as the initial cohorts of vaccinated women enter screening age and as we observe increasing empirical evidence of vaccine impact in the United States (10–12), the question of how to modify cervical cancer screening in HPV-vaccinated populations becomes critical.

Given the long, chronic course of cervical disease progression, spanning decades between initial HPV infection and invasive cancer, decisions regarding optimal cervical cancer prevention strategies must be made before their impact on long-term outcomes is observed. Policy-makers have increasingly relied on mathematical models to simulate the burden of disease in a population and to project both health and economic outcomes under realistic and "what if" scenarios. Using a disease simulation model of HPV and cervical cancer in US women, we evaluated how cervical cancer screening policies may be optimized in women vaccinated against HPV. In addition to assessing the cost-effectiveness of alternative strategies, we report both benefits and harms to showcase the clinical and public health trade-offs that may be useful to various decision-makers.

Methods

Mathematical Model

Using an individual-based microsimulation model of HPV and cervical cancer, we projected health and economic outcomes associated with screening in women vaccinated by the bivalent or quadrivalent vaccine (HPV-2 or HPV-4, respectively), or the nonavalent vaccine (HPV-9). Individual girls enter the model at an early age (ie, 9 years) prior to HPV acquisition and transition between mutually exclusive health states that represent clinically relevant stages of cervical disease (Supplementary Figure 1, available online) (13,14). Transitions to and from the HPV health states are governed by persistence of type-specific infection (ie, time since HPV acquisition) and can vary by factors such as age, history of prior HPV infection, and patterns of vaccination and screening. Given the individual-level simulation, the model can closely mirror complex screening algorithms and

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keeps track of each individual woman's health status and resource use over time, which are then aggregated at the population level.

Baseline model parameter values were estimated from large epidemiologic studies (13,15–17), and uncertain model parameters were calibrated to fit observed data from the United States, including HPV prevalence and type distribution among women with precancer and cancer (18–20). In order to reflect the uncertainty in the natural history inputs, we utilized the 50 top-fitting parameter sets for all analyses and calculated the expected value, as well as a range of values, for all outcomes. Descriptions of the model development process, including parameter estimation, model calibration, and model validation, have been previously published (13,14); details of model inputs and calibration results for this particular analysis are provided in the Supplementary Material (Supplementary Table 1 and Supplementary Figure 2, available online).

Strategies

Screening strategies were evaluated separately for women who were fully vaccinated with either HPV-2,-4 or HPV-9 (Table 1). In addition to the two current guidelines-based screening strategies involving cytology testing and cotesting, we also included options for primary HPV testing with HPV-16/18 genotype information, which was recently approved by the US Food and Drug Administration in women age 25 years and older. Strategies varied by the age of screening initiation, age of switching to a new test, and interval between routine screens. Triage and management approaches for screen-positive women were assumed to be consistent with current guidelines (1,21,22). In all scenarios, routine screening discontinued after age 65 years.

We assumed that the recommended full three-dose series of any of the three vaccines occurred at age 12 years, prior to HPV exposure, resulting in high (100%) efficacy against vaccine-targeted HPV-16 and -18 types, consistent with per-protocol clinical trial results (3–5). For women vaccinated with the nonavalent vaccine, we additionally assumed that efficacy against HPV types 31, 33, 45, 52, and 58 was 96.0%, consistent with recent reports from a phase III study (6). A lower-bound estimate of 90% efficacy against all vaccine-targeted HPV types was explored in sensitivity analysis. Vaccine-induced protection was assumed to be life-long for all vaccines, with the presumption that extended efficacy could be achieved with or without booster doses.

To identify the optimal screening strategy in these groups of vaccinated women, we assumed women perfectly complied with the screening interval assigned, as well as follow-up procedures. Input values for screening test characteristics were based on current data and were assumed to be unchanged in vaccinated cohorts (Supplementary Table 2, available online). In sensitivity analysis, we evaluated the impact of diagnostic error and precancer treatment effectiveness. Cost inputs included direct medical costs associated with screening, diagnostic colposcopy with biopsy, treatment of precancer and invasive cancer (eg, personnel, tests, procedures), and vaccination (eg, three doses, wastage, supplies, and administration), as well as patient time and transportation costs. The cost per dose for HPV-2,-4 and HPV-9 was $120 and $135, respectively, based on the US Centers for Disease Control and Prevention (public sector) cost (23).

Analysis

Main model outcomes included 1) health benefits, in terms of reductions in lifetime risk of cervical cancer and gains in quality-adjusted life-years (QALYs), reflecting both mortality and diminished quality of life due to cervical cancer; 2) lifetime costs, including intervention costs incurred, as well as cost offsets due to disease prevented; and 3) screening harms, in terms of the rate of colposcopy referral per 1000 women screened over the lifetime (1). Outcomes were calculated from the age of 21 years, the earliest age of screening initiation. In the base case, we conducted separate analyses for women vaccinated with HPV-2,-4 and with HPV-9, assuming vaccination status at the individual level is readily available. However, because individual-level vaccination status is not always known, we also examined scenarios in which a single population-based screening policy is chosen based on a heterogeneous mix of unvaccinated and vaccinated women to explore important thresholds of vaccination uptake at which screening policy changes may be warranted.

We used cost-effectiveness analysis as a guide to identify screening strategies that are good value for money for each vaccinated subgroup. After eliminating strategies that were more costly and less effective (ie, strongly dominated) or less costly and less cost-effective (ie, weakly dominated) than an alternative strategy, incremental cost-effectiveness ratios (ICER) were calculated as the additional cost divided by the additional health benefit associated with one strategy compared with the next less costly strategy. Across the 50 top-fitting parameter sets, the ICER was calculated as the ratio of the mean cost divided by the mean health effect (ie, ratio of the means) (24). We used a range of suggested cost-effectiveness thresholds (ie, $50 000, $100 000, and $200 000 per QALY gained) as a benchmark to indicate strategies that are good value for money (25). Consistent with US guidelines, we adopted a societal perspective and discounted costs and QALYs by 3% annually (26).

Results

Optimal Screening in Women Vaccinated With HPV-2 Or HPV-4

The trade-off of health benefits and costs for all 25 strategies evaluated among women who had been fully vaccinated with HPV-2 or HPV-4 in pre-adolescence is displayed in Figure 1 (numeric results are provided in Supplementary Table 3, available online). For the strategy of vaccination alone without screening, the mean reduction in lifetime cervical cancer risk was projected to be 64.6%, compared with no intervention; the addition of screening strategies considerably improved cancer benefit, ranging from 88% to 98% lifetime risk reduction. Both QALYs and lifetime costs increased with higher screening frequency and younger age of screening initiation.

Cytology-only screening every five years starting at age 35 years had the lowest cost-effectiveness ratio of $20 950 per QALY, compared with vaccination alone. At thresholds of $50 000 or $100 000 per QALY, optimal strategies involved five-year screening starting at age 30 years with either cytology or HPV testing, respectively. At a higher threshold of $200 000 per QALY, HPV testing every five years starting at age 25 years was the optimal strategy for women vaccinated with HPV-2 or HPV-4. Screening vaccinated women more frequently than every five years (irrespective of start age) or starting at the age of 21 years

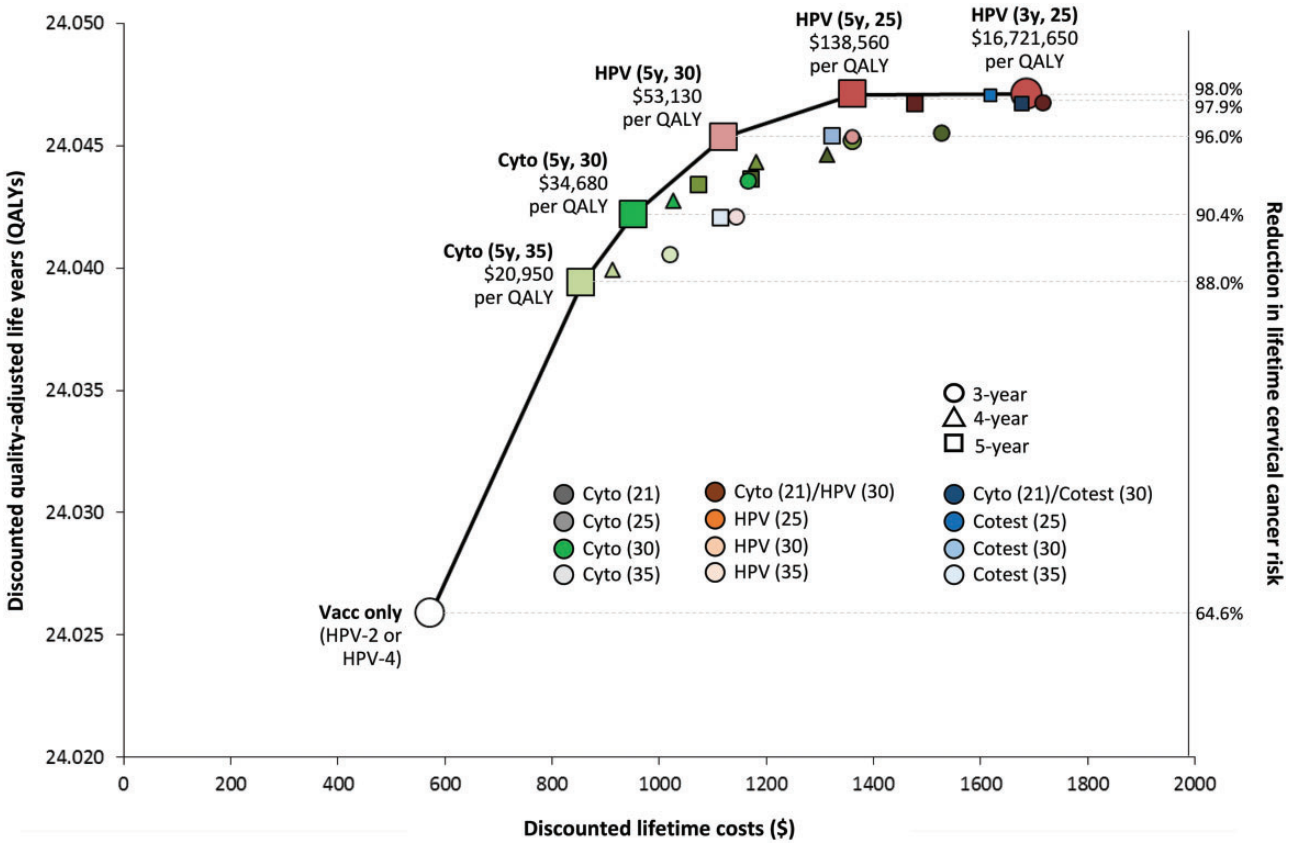

Figure 1. Health benefits and costs of cervical cancer screening strategies in women vaccinated with the bivalent or quadrivalent vaccine (human papillomavirus [HPV]–2, HPV-4). The figure displays the trade-off of quality-adjusted life-years (QALYs; **left y-axis**) and reductions in lifetime cervical cancer risk (**right y-axis**) against lifetime costs (**x-axis**) for each of the screening strategies. The **white circle** represents no screening (ie, vaccination only). The **colors** represent screening test: **Green** indicates cytology testing ("Cyto"); **red** indicates primary HPV testing ("HPV"); **blue** indicates cytology and HPV cotesting ("Cotest"). The **color shades** represent the age of screening initiation: **Darkest** indicates age 21 years (with or without a switch to another primary test); **next darkest** indicates age 25 years; **lighter** indicates age 30 years; **lightest** indicates age 35 years. The **shapes** represent screening interval: **Circle** indicates three-year screening; **triangle** represents four-year screening; **square** represents five-year screening. For all scenarios, routine screening ends at age 65 years. The **curve** indicates the strategies that are efficient; the incremental cost-effectiveness ratios of strategies on the curve represent the increase in mean lifetime cost divided by the increase in mean QALYs compared with the next less costly strategy, across 50 top-fitting parameter sets. Both QALYs and lifetime costs are discounted at 3% per year. HPV = human papillomavirus; QALY = quality-adjusted life-year.

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(irrespective of frequency) was either not cost-effective or had cost-effectiveness ratios that exceeded $200 000 per QALY gained. Importantly, the currently recommended strategies of cytology testing every three years starting at age 21 years with or without a switch to cotesting at age 30 years were inefficient, and under no conditions was cotesting attractive.

Optimal Screening in Women Vaccinated With HPV-9

The mean reduction in lifetime risk of cervical cancer was 85.3% in women vaccinated with HPV-9, compared with no intervention; with screening, cancer reductions ranged from 91% to 99% (Figure 2; Supplementary Table 4, available online). Given the lower baseline disease risk in women vaccinated with HPV-9, the optimal screening strategies involved later start ages and lower frequencies than for women vaccinated with HPV-2 or HPV-4. Furthermore, only strategies that involved primary HPV testing were efficient. For example, at a threshold of $50 000 per QALY, HPV testing every 10 years starting at age 35 years was the most cost-effective strategy with a ratio of $40 210 per QALY, compared with one-time HPV testing at age 40 years, which had a lower ratio of $18 010 per QALY. At a higher threshold of $200 000 per QALY, HPV testing every 10 years was still optimal but at an earlier start age of 30 years. Strategies that started earlier (age 21 or 25 years) and/or were more frequent than every 10 years had exceedingly high cost-effectiveness ratios (ie, above $200 000 per QALY) or were dominated, including HPV testing every three years starting at age 25 years, a strategy recommended by some societies (22).

Cancer Reduction vs Colposcopy Rate

We further compared the relative harms and benefits in terms of colposcopy referrals and reductions in lifetime cervical cancer risk for the screening strategies found to be cost-effective, as well as the current guidelines-based strategies (Figure 3). Not surprisingly, more intensive strategies were associated with higher colposcopy referrals rates and also higher cancer benefit. In women vaccinated with HPV-2 or HPV-4, colposcopy rates for strategies that were found to be efficient (ie, not dominated) ranged from 249 to 880 per 1000 women screened (Figure 3, top panel). Screening that involved HPV testing, either alone or as part of cotesting, was associated with higher colposcopy rates than cytology-only strategies.

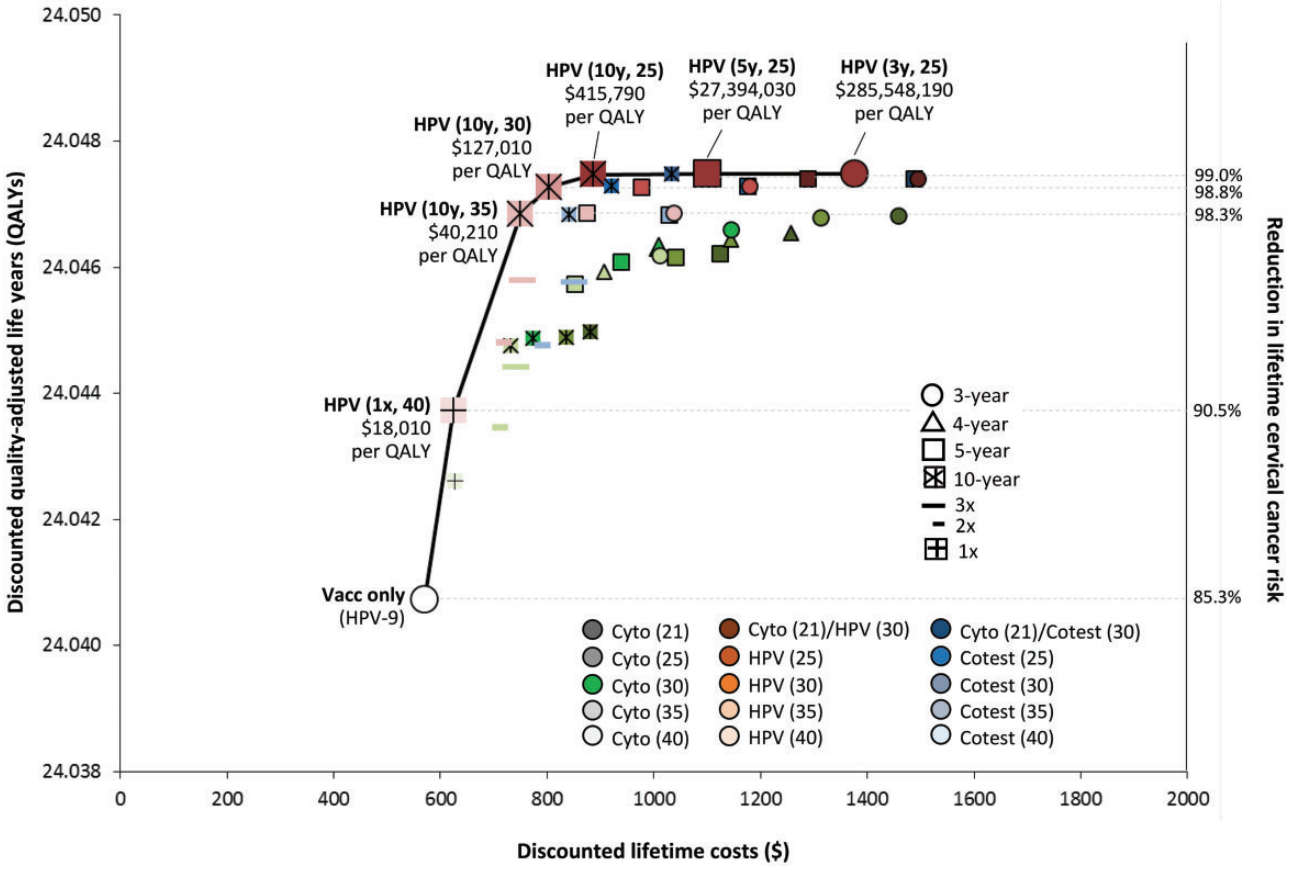

Figure 2. Health benefits and costs of cervical cancer screening strategies in women vaccinated with the nonavalent vaccine (human papillomavirus [HPV]-9). The figure displays the trade-off of quality-adjusted life-years (QALYs; **left y-axis**) and reductions in lifetime cervical cancer risk (**right y-axis**) against lifetime costs (**x-axis**) for each of the screening strategies. The **white circle** represents no screening (ie, vaccination only). The **colors** represent screening test: **Green** indicates cytology testing ("Cyto"); **red** indicates primary HPV testing ("HPV"); **blue** indicates cytology and HPV cotesting ("Cotest"). The **color shades** represent the age of screening initiation: **Darkest** indicates age 21 years (with or without a switch to another primary test); **next darkest** indicates age 25 years; **medium** indicates age 30 years; **lighter** indicates age 35 years; **lightest** indicates age 40 years. The **shapes** represent screening interval: **Circle** indicates three-year screening; **triangle** represents four-year screening; **square** represents five-year screening; **asterisk** represents 10-year screening; **long dash** represents three-time screening over the lifetime; **short dash** represents two-time screening over the lifetime; **cross** indicates one-time screening over the lifetime. For all scenarios, routine screening ends at age 65 years. The curve indicates the strategies that are efficient; the incremental cost-effectiveness ratios of strategies on the **curve** represent the increase in mean lifetime cost divided by the increase in mean QALYs compared with the next less costly strategy, across 50 top-fitting parameter sets. Both QALYs and lifetime costs are discounted at 3% per year. HPV = human papillomavirus; QALY = quality-adjusted life-year.

In women vaccinated with HPV-9, colposcopy rates were far lower, ranging from 11 to 228 per 1000 women screened, among the efficient screening strategies (Figure 3, bottom panel). Although at low absolute rates, shifting from HPV testing one time at age 40 years to every 10 years starting at age 35 years increased the colposcopy rate seven-fold (from 11 to 87 per 1000 women) but also increased cancer benefit (from 90% to 98% reduction in lifetime cancer risk). For the remaining efficient strategies involving higher screening frequency and/or earlier screening initiation ages, the higher colposcopy rates were accompanied by minimal improvements in cancer benefit. In both vaccinated populations, the two current guidelines-based strategies had lower benefit and higher colposcopy rates than alternative strategies.

Sensitivity Analysis

All analyses were conducted with 50 calibrated parameter sets to reflect the underlying uncertainty in the natural history data, enabling a range of results to be reported (Supplementary Tables 3 and 4, available online). We found that the rank ordering of the screening strategies was stable over the 50 sets in both HPV-2,-4- and HPV-9-vaccinated populations and that the optimal strategies identified under each cost-effectiveness threshold were unchanged in the majority of simulations. Results were also robust when we varied vaccine efficacy, diagnostic test performance, and precancer treatment effectiveness, with only slight changes in the cost-effectiveness ratios. The only exception was when efficacy against all vaccine-targeted HPV types in HPV-9 was reduced, in which the optimal initiation ages of 35 and 30 years in the base case scenario shifted to earlier ages of 30 years (ie, $35 310 per QALY) and 25 years (ie, $128 780 per QALY) (Supplementary Figure 3, available online).

When we explored scenarios of mixed vaccination status within the population, we found that screening every five years remained the optimal interval at cost-effectiveness thresholds ranging from $50 000 to $200 000 per QALY when HPV-2 or HPV-4 uptake was at 50% or greater (Table 2). With increasing proportions of women vaccinated with HPV-2 or HPV-4, optimal

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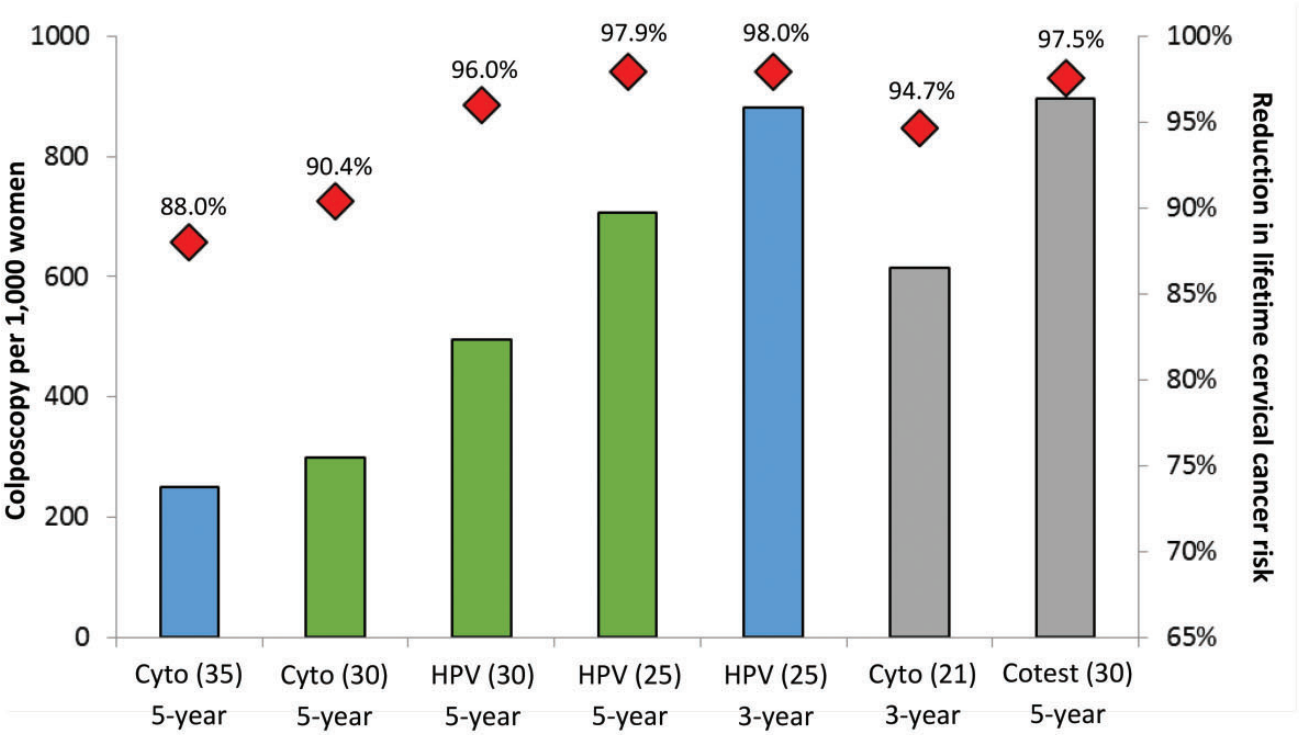

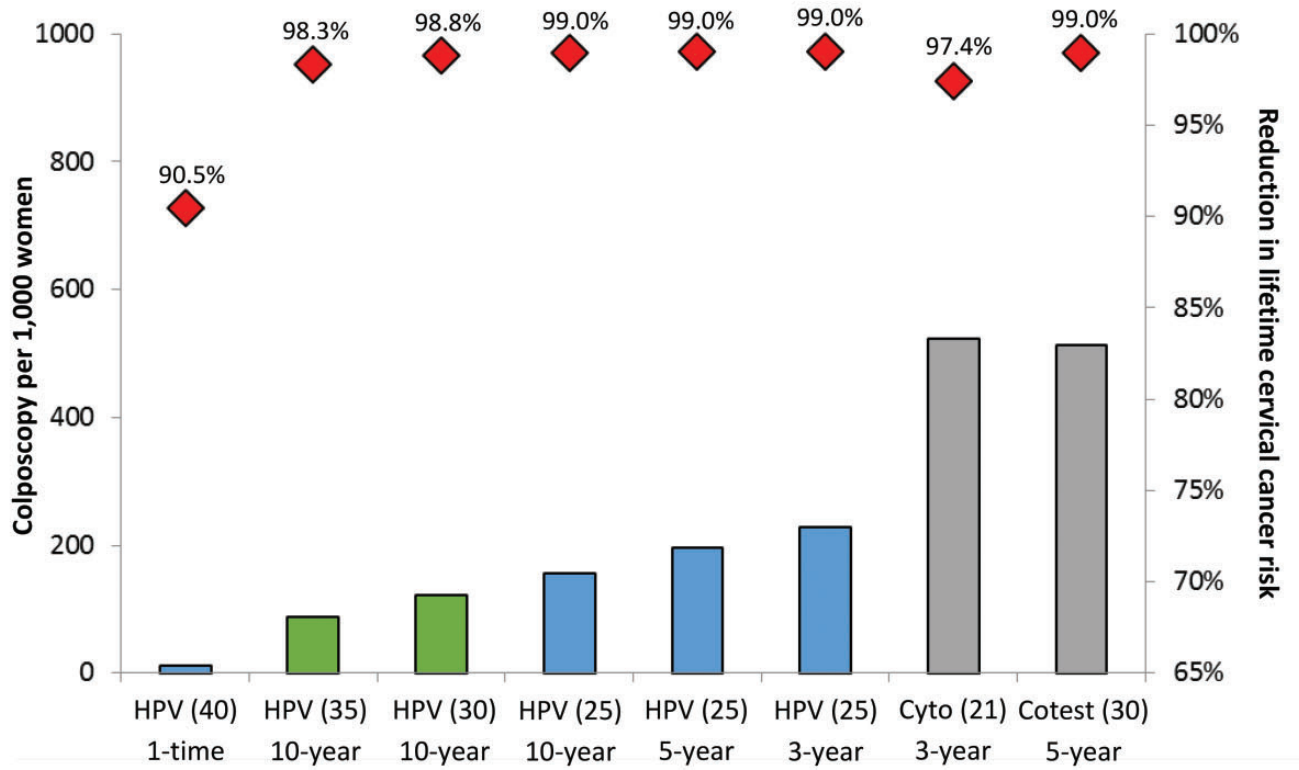

Figure 3. Harms vs benefits of efficient strategies. The figure displays the trade-off of colposcopy referral rates (**left y-axis**) and reductions in lifetime cervical cancer risk (**right y-axis**) for screening strategies that were efficient (ie, on the efficiency frontier) in women vaccinated with the bivalent or quadrivalent vaccine (**top**) or the nonavalent vaccine (**bottom**). **Bars** represent the number of colposcopy referrals per 1000 women over the lifetime, starting at age 21 years: **Green bars** indicate strategies that are considered cost-effective according to benchmarks of good value for money in the United States (25); **gray bars** indicate current US guidelines-based strategies (1,2); and **blue bars** indicate the remaining efficient strategies. The **red diamonds** represent the reductions in lifetime cervical cancer risk associated with each strategy compared with no intervention.

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Table 2. Optimal screening strategies in partially vaccinated populations, under different cost-effectiveness thresholds*

Proportion of population vaccinated	$50 000 per QALY gained (% cost-effective)†	$100 000 per QALY gained (% cost-effective)†	$200 000 per QALY gained (% cost-effective)†
Vaccination with HPV-2,-4			
50% unvaccinated; 50% HPV-2,-4	Cytology, age 25 y5-y (98)	HPV, age 25 y5-y (90)	HPV, age 25 y5-y (100)
25% unvaccinated; 75% HPV-2,-4	HPV, age 30 y5-y (80)	HPV, age 25 y5-y (74)	HPV, age 25 y5-y (100)
10% unvaccinated; 90% HPV-2,-4	HPV, age 30 y5-y (74)	HPV, age 30 y5-y (100)	HPV, age 25 y5-y (100)
0% unvaccinated; 100% HPV-2,-4	Cytology, age 30 y5-y (94)	HPV, age 30 y5-y (100)	HPV, age 25 y5-y (98)
Vaccination with HPV-2,-4, -9			
25% unvaccinated; 50% HPV-2,-4; 25% HPV-9	HPV, age 30 y10-y (100)	HPV, age 25 y10-y (96)	HPV, age 25 y10-y (100)
0% unvaccinated; 50% HPV-2,-4; 50% HPV-9	HPV, age 30 y10-y (100)	HPV, age 30 y10-y (88)	HPV, age 25 y10-y (98)
0% unvaccinated; 25% HPV-2,-4; 75% HPV-9	HPV, age 35 y10-y (100)	HPV, age 30 y10-y (98)	HPV, age 25 y10-y (80)
0% unvaccinated; 10% HPV-2,-4; 90% HPV-9	HPV, age 35 y10-y (100)	HPV, age 30 y10-y (82)	HPV, age 30 y10-y (100)
0% unvaccinated; 0% HPV-2,-4; 100% HPV-9	HPV, age 35 y10-y (94)	HPV, age 35 y10-y (100)	HPV, age 30 y10-y (94)

*Table indicates the optimal screening strategy (ie, primary screening test, screening interval, age of screening initiation) under different patterns of human papillomavirus (HPV) vaccination uptake in the population. We used a range of cost-effectiveness thresholds (ie, $50 000 to $200 000 per QALY) as benchmarks for good value for money and to determine the optimal strategies under each scenario (ie, the most effective strategy with an incremental cost-effectiveness ratio less than the indicated threshold) (25). Blue shading indicates strategies in which screening initiation occurs at age 25 years; yellow shading, age 30 years; green shading, age 35 years. HPV-2, HPV-4, and HPV-9 refer to the bivalent, quadrivalent, and nonavalent HPV vaccines, respectively. HPV = human papillomavirus.
†Percent cost-effective refers to the proportions of simulations across the 50 top-fitting parameter sets in which the specified strategy was optimal for the given cost-effectiveness threshold.

screening initiation shifted from age 25 to 30 years and primarily involved HPV testing. At the highest cost-effectiveness threshold of $200 000 per QALY, the optimal strategy consistently was HPV testing starting at age 25 years. When also considering uptake of HPV-9, HPV testing at a 10-year interval was uniformly optimal across all uptake assumptions and cost-effectiveness thresholds (Table 2). At higher proportions of women vaccinated with HPV-9, the screening start age shifted to later ages.

Discussion

This analysis supports a reassessment of cervical cancer screening policies in women who have been vaccinated against HPV. We found that, given the expected lower risk of cervical cancer in HPV-vaccinated women, screening can be modified to start at later ages, occur at decreased frequency, and involve primary HPV testing. In particular, for women who received the full three doses of HPV-2 or HPV-4 in pre-adolescence, screening every five years starting at age 25 or 30 years with cytology or HPV testing was optimal at recommended cost-effectiveness thresholds of $50 000 to $200 000 per QALY gained. In women fully vaccinated with HPV-9, optimal screening extended to every 10 years starting at age 30 or 35 years with HPV testing. Importantly, these less-intensive strategies provided similar or higher benefit at lower cost (and lower harms as measured by colposcopy rates) than keeping with current screening guidelines in HPV-vaccinated women, indicating that revisions in screening policies for vaccinated women are warranted. In both vaccinated populations, primary HPV testing was competitive or preferred over cytology testing and cotesting strategies. In some scenarios, even when administered at lower intensity, HPV testing outperformed (ie, yielded greater health benefit than) cytology alone; this is because of the higher clinical sensitivity of HPV testing vs cytology, which offset the lower benefit associated with a later start age and/or less frequent screening.

It is noteworthy that the screening strategies in HPV-vaccinated women led to nearly equivalent health benefits in terms of QALYs and reductions in lifetime cancer risk as the screening intensity increased, especially in women vaccinated with the nonavalent vaccine. In order to assess the robustness of strategies with such marginal health benefits, we conducted all analyses using 50 calibrated parameter sets as a form of probabilistic sensitivity analysis and found that our main findings were very stable. Optimal screening strategies also remained unchanged when we altered vaccine efficacy and screening effectiveness. Only when vaccine efficacy was decreased for all high-risk HPV types in HPV-9 did the base case screening initiation shift to an earlier age; however, the 10-year screening interval in women vaccinated with HPV-9 remained most efficient throughout.

Our findings for women vaccinated with HPV-2 or HPV-4 are consistent with previous model-based studies that found opportunities to screen less intensively with later start ages, longer intervals between screens, and HPV testing instead of cytology (27,28). Our study contributes to this literature in reassessing the value of HPV testing in vaccinated women after its recent approval for use as a primary screening test in the United States, and as the first US-based analysis to evaluate screening in women vaccinated with HPV-9.

Our analysis has important limitations. To guide policy, we focused on scenarios in which women had been fully vaccinated (ie, received all three doses) in pre-adolescence; therefore, generalizability to women who are vaccinated at later ages or who receive less than three doses is unclear, although short-term efficacy data indicate that two-dose, and even one-dose, vaccination is promising (29,30). Furthermore, we assumed that women are fully compliant to screening. In reality, behaviors and practice with respect to screening uptake, diagnostic work-up, and treatment may vary differentially based on vaccination status, which may impact the relative cost-effectiveness of the screening strategies. Analyses will need to be revisited as data on screening practice in HPV-vaccinated women emerge.

This analysis also focused on women with a known history of HPV vaccination in pre-adolescence, whereas in many settings, including the United States, HPV vaccination status at the individual level may not be readily available (ie, type of vaccine received, age at vaccination, and number of doses). In such settings, there may be opportunity to optimize screening based on vaccination uptake at the population level. Our sensitivity analysis exploring universal screening policies in partially

vaccinated populations was crude given the exclusion of herd immunity effects among unvaccinated women, resulting in a likely underestimation of population-level benefit from HPV vaccination. Nonetheless, our findings support shifting to less intensive screening than currently recommended even at moderate vaccination uptake rates in the United States. Future analyses leveraging HPV transmission models that reflect vaccination uptake for both sexes at different ages and across different birth cohorts will need to incorporate the effects of herd immunity to identify optimal screening strategies with greater specificity. It is noteworthy that selecting a universal cervical cancer screening policy that aims to target the average risk profile in the population without being able to tailor policies based on known vaccination status may lead to inefficiencies and forgone health benefits (ie, among those who are not vaccinated and do not benefit from herd immunity); understanding the value of knowing an individual woman's vaccination history will be important in future work as we confront the heterogeneity in risk that is being introduced in a population with mixed vaccination status.

Our analysis did not consider potential changes in screening test performance in vaccinated women. It is hypothesized that the test performance of cytology may diminish as HPV prevalence decreases as a result of vaccination and as fewer cytologic samples are positive; these changes would only strengthen our findings, which already favor primary HPV testing in the majority of scenarios.

We did not capture other health benefits from HPV vaccination, such as prevention of anogenital warts or other noncervical HPV-related cancers. Although the inclusion of these benefits would improve the overall cost-effectiveness of HPV vaccination, they are not expected to have any impact on the comparative or cost-effectiveness of the competing cervical cancer screening strategies. We only reported on a single measure of screening harms, colposcopy referrals, which has been used in guidelines deliberations (1,2). Yet other adverse outcomes, such as preterm births associated with precancer treatment and decreased quality of life associated with positive screening results, have also been reported (31–33). This analysis suggests that modifying screening in HPV-vaccinated women will result in a substantial decrease in screening procedures, and therefore inclusion of these adverse outcomes would only strengthen the argument to de-intensify screening in HPV-vaccinated women.

Our analysis clearly indicates opportunities to revise cervical cancer screening policies in HPV-vaccinated women. For women vaccinated with any of the approved HPV vaccines early in adolescence—and even in the current US population with only partial vaccination uptake—our model-based projections suggest that less-intensive screening algorithms can provide greater health benefit at lower harms and costs than current screening guidelines, which do not differentiate recommendations based on HPV vaccination status.

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References

1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*. 2012;62(3):147–172.
2. Moyer VA. Screening for Cervical Cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;156:880–891.
3. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007;356(19):1915–1927.
4. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): Final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374(9686):301–314.
5. Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: Final analysis of a long-term follow-up study up to 9.4 years post-vaccination. *Hum Vaccin Immunother*. 2014;10(8):2147–2162.
6. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711–723.
7. Petrosky E, Bocchini JA Jr, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):300–304.
8. Reagan-Steiner S, Yankey D, Jeyarajah J, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years–United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(29):784–792.
9. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: An ecological study. *Lancet*. 2011;377(9783):2085–2092.
10. Hariri S, Bennett NM, Niccolai LM, et al. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States - 2008-2012. *Vaccine*. 2015;33(13):1608–1613.
11. Hariri S, Markowitz LE, Dunne EF, Unger ER. Population impact of HPV vaccines: Summary of early evidence. *J Adolesc Health*. 2013;53(6):679–682.
12. Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV after introduction of the vaccination program in the United States. *Pediatrics*. 2016;137(3):1–9.
13. Campos NG, Burger EA, Sy S, et al. An updated natural history model of cervical cancer: Derivation of model parameters. *Am J Epidemiol*. 2014;180(5):545–555.
14. Kim JJ, Campos NG, Sy S, et al. Inefficiencies and high-value improvements in US cervical cancer screening practice: A cost-effectiveness analysis. *Ann Intern Med*. 2015;163(8):589–597.
15. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: Critical role of duration of infection. *J Natl Cancer Inst*. 2010;102(5):315–324.
16. Herrero R, Hildesheim A, Rodriguez AC, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. *Vaccine*. 2008;26(37):4795–4808.
17. Munoz N, Mendez F, Posso H, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *J Infect Dis*. 2004;190(12):2077–2087.
18. Wheeler CM, Hunt WC, Cuzick J, et al. A population-based study of human papillomavirus genotype prevalence in the United States: Baseline measures prior to mass human papillomavirus vaccination. *Int J Cancer*. 2013;132(1):198–207.
19. Joste NE, Ronnett BM, Hunt WC, et al. Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):230–240.
20. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA*. 2007;297(8):813–819.
21. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2013;17(5 Suppl 1):S1–S27.
22. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. *Gynecol Oncol*. 2015;136(2):178–182.
23. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention. CDC vaccine price list. http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/. Accessed March 14, 2016.
24. Stinnett AA, Paltiel AD. Estimating CE ratios under second-order uncertainty: The mean ratio versus the ratio of means. *Med Decis Making*. 1997;17(4):483–489.

25. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796–797.
26. Gold MR, Siegel JE, Russel LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.
27. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus (HPV) DNA testing and HPV-16,18 vaccination. *J Natl Cancer Inst*. 2008;100(5):308–320.
28. Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA*. 2003;290(6):781–789.
29. Kreimer AR, Rodriguez AC, Hildesheim A, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. *J Natl Cancer Inst*. 2011;103(19):1444–1451.
30. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: Combined analysis of data from the Costa Rica Vaccine and PATRICIA Trials. *Lancet Oncol*. 2015;16(7):775–786.
31. Arbyn M, Kyrgiou M, Simoens C, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: Meta-analysis. *BMJ*. 2008;337:a1284.
32. Insinga RP, Glass AG, Myers ER, Rush BB. Abnormal outcomes following cervical cancer screening: Event duration and health utility loss. *Med Decis Making*. 2007;27(4):414–422.
33. Korfage IJ, Essink-Bot ML, Westenberg SM, Helmerhorst T, Habbema JD, van Ballegooijen M. How distressing is referral to colposcopy in cervical cancer screening? A prospective quality of life study. *Gynecol Oncol*. 2014;132(1):142–148.